Practitioner's Docket No. 09262-026-9448

CHAPTER II

Preliminary Classification:

Proposed Class:

Subclass:

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.'" M.P.E.P., § 601, 7th ed.

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/GB99/00876	19 March 1999	19 March 1998
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

DIAGNOSIS OF SPONGIFORM OR DE-MYELINATING DISEASE
TITLE OF INVENTION

EBRINGER, Alan
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date 18 Sept. 2000, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL618987577US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

JUDY KEELEY
(type or print name of person mailing paper)

Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing—See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

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2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
☐*	TOTAL CLAIMS 15	-20=	-0-	× $18.00=	$ -0-
	INDEPENDENT CLAIMS 1	-3=	-0-	× $78.00=	-0-
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an international preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 ☒ U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $760.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 ☒ where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) $840.00				
	Total of above Calculations				= $840.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				-
	Subtotal				
	Total National Fee				$ $840.00
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL	Total Fees enclosed				$ $840.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. ☒ A check in the amount of $840.00 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

***WARNING:** *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____ *(Date).*

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☐ is transmitted herewith.

b. ☒ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____ *(Date).*

d. ☐ will follow.

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: *The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.*

a. ☒ are transmitted herewith. *

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____ *(Date).*

c. ☐ have not been transmitted as

i. ☐ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): _____.

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☒ is not required as the amendments were made in the English language.

c. ☐ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☒ Annex(es) to the international preliminary examination report

a. ☒ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☒ A translation of the annexes to the international preliminary examination report

a. ☐ is transmitted herewith.

b. ☒ is not required as the annexes are in the English language.

*The claims were amended during the international examination. Claims 1 through 13 are amended, and claims 13 through 15 are added as shown in the International Preliminary Examination Report. The claims are further hereby amended to delete

multiple dependencies, as shown in the attached claims. Please further amend this application to add the following to the specification on page 1, after the title: "This application is a continuation-in-part of U.S. patent application serial no. 09/269,607 filed 07/26/99, claiming priority from PCT/GB97/02267. The disclosure of 09/269,607 is incorporated herein by reference."

10. ☒ An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

    a. ☐ was previously submitted by applicant on _____ *(Date)*.

    b. ☐ is submitted herewith, and such oath or declaration

        i. ☐ is attached to the application.

        ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

    c. ☒ will follow.

II. Other document(s) or information included:

11. ☒ An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

    a. ☒ is transmitted herewith.

    b. ☐ has been transmitted by the International Bureau.
    Date of mailing (from form PCT/IB/308): _____.

    c. ☐ is not required, as the application was searched by the United States International Searching Authority.

    d. ☐ will be transmitted promptly upon request.

    e. ☐ has been submitted by applicant on _____ *(Date)*.

12. ☒ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

    a. ☐ is transmitted herewith.

    Also transmitted herewith is/are:

    ☐ Form PTO-1449 (PTO/SB/08A and 08B).

    ☐ Copies of citations listed.

    b. ☒ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

    c. ☐ was previously submitted by applicant on _____ *(Date)*.

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

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14. ☒ Additional documents:
    a. ☐ Copy of request (PCT/RO/101)
    b. ☒ International Publication No. WO 99/47932
        i. ☐ Specification, claims and drawing
        ii. ☒ Front page only
    c. ☐ Preliminary amendment (37 C.F.R. § 1.121)
    d. ☒ Other
        International Search Report
        International Preliminary Examination Report

15. ☒ The above checked items are being transmitted
    a. ☒ before 30 months from any claimed priority date.
    b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 03-3975.

☒ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

☒ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☒ 37 C.F.R. § 1.17 (application processing fees)

☒ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☒ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

DAVID H. JAFFER

(type or print name of practitioner)

PILLSBURY MADISON & SUTRO LLP

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Customer No.:

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: EBRINGER, Alan		Attorney Docket:	09262-0269448
Serial No.: 09/646,579		International Application No.:	PCT/GB99/00876
Filed: September 18, 2000		International Filing Date:	19 March 1999
		Priority Date:	19 March 1998

For **DIAGNOSIS OF SPONGIFORM OR DE-MYELINATING DISEASE**

Commissioner of Patents and Trademarks
BOX PCT
Washington, D.C. 20231

AMENDMENT

Dear Sir:

In response to the Notice to File Missing Parts mailed **7 November 2000**, please amend the application as follows:

In the Specification

Page 1, after the title, insert:

"This application is a continuation-in-part of U.S. patent application serial number 09/269,607 filed July 26, 1999, claiming priority from PCT/GB97/02267. The disclosure of 09/269,607 is incorporated herein by reference."

In the Claims

Replace claims 1 through 13 with claims 1 through 15 from Pages 6 through 8 of the Amended Sheets.

Further amend the claims on Pages 6 through 8 of the Amended Sheets to delete multiple dependencies as follows:

Claim 3, page 6, line 1: Change "1 or 2" to --1--.

Claim 4, page 6, line 1: Change "1, 2, or 3" to --1--.

Claim 5, page 6, line 1: Change "any of claims 1 to 4" to --claim 1--.

Claim 6, page 6, line 1: Change "any of claims 1 to 4" to --claim 1--.

Claim 7, page 6, line 1: Change "any of claims 1 to 4" to --claim 1--.

Claim 8, page , line 1: Change "any of the preceding claims" to -- claim 1--.

Claim 9, page 7, line 1: Change "any of claims 1 to 8" to --claim 1--.

Claim 10, page 7, line 1: Change "1, 2, or 3," to --1,--.

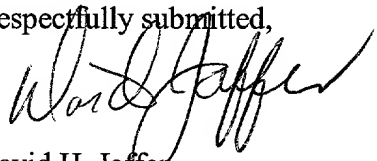
Claim 13, page 7, line 1: Change "10, 11, or 12" to --10--.

Claim 15, page , line 1: Delete "or according to claim 13 or 14,".

Conclusion

The Examiner is respectfully invited to contact the undersigned with questions.

Respectfully submitted,



PILLSBURY MADISON & SUTRO
2550 Hanover Street
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(650) 233-4510

David H. Jaffer
Reg. No. 32,243

CERTIFICATE OF MAILING

I, Judy Keeley, hereby certify that this correspondence is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents and Trademarks, BOX PCT, Washington, D.C. 20231.

Date: December 18, 2000

CLAIMS

1. A method for detecting a de-myelinating disease or spongiform encephalopathy in mammals which comprises testing a biological sample obtained from the mammal for IgA antibodies which bind to an *Acinetobacter* antigen.

2. A method according to claim 1, in which the *Acinetobacter* is one which presents to the mammal an antigen which exhibits molecular mimicry with the myelin of the mammal.

3. A method according to claim 1 ~~or 2~~, in which the antibodies are indicative of prior infection by *Acinetobacter calcoaceticus*.

4. A method according to claim 1, ~~2 or 3~~, in which the antibodies tested for are antibodies which bind to an epitope present in or derived from the *Acinetobacter* species or to a prepared peptide sequence corresponding thereto.

5. A method according to any of claims 1 ~~to 4~~, in which the disease tested for is bovine spongiform encephalopathy.

6. A method according to any of claims 1 ~~to 4~~, in which the disease tested for is multiple sclerosis in humans.

7. A method according to any of claims 1 ~~to 4~~, in which the disease tested for is Creutzfeldt-Jacob disease in humans.

8. A method according to claim 1 ~~any of the preceding claims~~ in which antibodies are assayed and a positive result is indicated by levels of antibodies at least about two standard deviations above that of control samples.

9. A test kit for use with a method according to any of claims 1 ~~to 8,~~ in which the test antigen is the whole *Acinetobacter* organism or at least one prepared peptide sequence corresponding to an *Acinetobacter* epitope, said test kit including a secondary antibody against the human, bovine, or other mammalian IgA.

10. A method according to claim 1, ~~X or 3,~~ in which the antibodies tested for are antibodies which bind to a peptide sequence conformationally similar to an *Acinetobacter* epitope.

11. A method according to claim 10, in which the epitope is the peptide sequence ISRFAWGEV.

12. A method according to claim 10, in which the epitope contains the peptide sequence RFSAWGAE.

13. A test kit for use with a method according to claim 10, ~~X, or 12,~~ in which the test antigen is a peptide sequence which is conformationally sufficiently similar to an *Acinetobacter* epitope to bind to the relevant antibodies, said test kit including a secondary antibody against the human, bovine, or other mammalian IgA.

14. A test kit according to claim 13, comprising a peptide having the sequence RFSAWGAE or ISRFAWGEV.

15. A test kit according to claim 9, ~~or according to claim 13 or 14,~~ in which the secondary antibody is a rabbit anti-human IgA or rabbit anti-bovine IgA.

DIAGNOSIS OF SPONGIFORM OR DE-MYELINATING DISEASE

This invention relates to the diagnosis of de-myelinating diseases and spongiform encephalopathies in animals and humans.

In our copending application WO 98/13694 we have disclosed a new diagnostic test for spongiform encephalopathies and other de-myelinating conditions in mammals. The test disclosed in our prior application is based on a model of the genesis of this pathological state which is applicable to the various forms in which it is manifest in humans and animals. In relation to the bovine spongiform disease this model provides an alternative to the current theory based on the formation of prions. Briefly, this new model is based on the phenomenon of molecular mimicry according to which mammals exposed to certain bacteria having peptide sequences which mimic myelin peptides experience an auto-immune reaction. In our prior application we indicated that human de-myelinating diseases were also open to the same explanation according to our new model disclosed therein.

According to the present invention, a method for detecting a de-myelinating disease or spongiform encephalopathy in mammals comprises testing a biological sample obtained from the mammal for IgA antibodies indicative of infection by an *Acinetobacter* species. We believe that infective micro-organisms of these species present to the mammal an antigen which exhibits molecular mimicry with the myelin of the mammal. The phenomenon of molecular mimicry has been explained in our above-mentioned prior

application WO 98/13694, the contents of which are hereby incorporated by reference.

We have now confirmed the presence of elevated levels of certain antibodies in human sera of patients suffering from multiple sclerosis (MS). These are the IgA antibodies to *Acinetobacter* species e.g. *Acinetobacter calcoaceticus*, the same organisms for which antibodies were previously found in BSE sera. Similar results have been obtained for Creutzfeldt-Jakob disease (CJD). Tests for antibodies in sera from patients who had died of CJD also show increased levels, this being especially marked for the IgA antibody sub-class. The same IgA specificity also applies to bovine sera used for the tests described in our above-mentioned copending application.

It is clear that humans suffering from MS and CJD and cows suffering from BSE all have very significantly raised levels of *Acinetobacter calcoaceticus* IgA antibodies in their blood. Tests for such antibodies in sera from living subjects at an early stage make it possible to identify those liable to develop these diseases. The present invention opens up the opportunity of early treatment of these infections e.g. by use of an appropriate antibiotic to prevent further auto-immune attack on the subjects' own myelin.

As also indicated in our application WO 98/13694, *Acinetobacter calcoaceticus* is one species of *Acinetobacter* which provides an antigen which stimulates the formation of antibodies which cross-react with the mammalian myelin . Antibodies have been demonstrated to react with several strains of this species including 17905, AC606, SP13TV, 105/85, and 11171. These strains are in the

Reference Centre for Acinetobacter species held by Dr Kevin Towner, Public Health Laboratory, University of Nottingham, U.K.

In carrying out the present invention, the test is for antibodies which bind to an epitope present in or derived from the *Acinetobacter* species. The antigen used in the test may be the whole organism or at least one prepared peptide sequence corresponding to an *Acinetobacter* epitope. Alternatively, peptide sequences may be used which have minor variations in amino-acid sequence from the above-mentioned epitopes or prepared peptides but are conformationally sufficiently similar to them that they also bind to the relevant antibodies. For example, peptides having the sequence RFSAWGAE or ISRFAWGEV may be used.

A test kit for use according to the invention therefore contains at least one test antigen as just indicated. In order to reveal IgA antibodies the kit also contains a secondary antibody against the human, bovine, or other mammalian IgA.

As indicated in WO 98/13694, antibodies are assayed and a positive result is indicated by levels of antibodies at least about two standard deviations above that of control samples.

In view of the greater specificity of the IgA antibodies in the immune response it may be concluded that the mechanism of infection with *Acinetobacter* is via the mucous membranes of the body, the primary sites being the gut or the nasal passages. Since a further correlation has been observed between MS sufferers and patients with major sinus infections, it is probable that the nasal passages

EXAMPLE

The assay for the above mentioned organisms is described in our co-pending application mentioned above. The improved method used herein is as follows:-

ELISA TEST

1) Aliquots of 200 ul of the diluted suspension of *Acinetobacter calcoaceticus* (NCIMB 10694, Aberdeen) grown in nutrient broth are absorbed onto 96 well flat bottomed rigid polystyrene microtitre plates overnight at 4°C.
2) The plates are then washed 3 times with phosphate buffered saline (PBS), 0.1% (v/v) Tween 20.
3) Aliquots of 200 µl of blocking solution (0.2% w/v ovalbumin, 0.1% v/v Tween 200 in PBS is added to each well and incubated for one hour at 37°C.
4) The plates are then washed 3 times with PBS.Tween 20.
5) Aliquots of 200 µl serum samples (test or control) diluted 1/200 in PBS. Tween 20 is added and incubated for 2 hours at 37°C.
6. The plates are then washed 3 times with PBS.Tween 20.
7) Aliquots of 200 µl of peroxidase conjugated rabbit anti-human IgA or rabbit anti-cow Iga , diluted 1/4000 (cow) (or 1/500 for human) with PBS.Tween 20 are added and incubated for 2 hours at 37°C.
8) The plates are then washed 3 times with PBS.Tween 20.

9) The development of the colorimetric assay takes place at room temperature for 20 minutes, after the addition of 200 µl per well of 0.5 mg/ml (2,2'-azinobis(3-ethylbenz-thiazoline-6-sulphonic acid) in citrate/phosphate buffer, pH 4.1, containing 0.98 mM hydrogen peroxide.

10) the reaction is then stopped with 100 µl of 2 mg/ml sodium fluoride and optical densities measured at a wavelength of 630 nm with a micro-ELISA plate reader.

Results for MS and CJD are shown in the attached Figure 1 and those for BSE are shown in Figure 2. These give the titres of IGA *Acinetobacter* antibodies in MS and CJD sera, BSE sera, and control sera. The dashed line represents the 95% confidence limits of the controls.

AMENDED SHEET

CLAIMS

1. A method for detecting a de-myelinating disease or spongiform encephalopathy in mammals which comprises testing a biological sample obtained from the mammal for IgA antibodies which bind to an *Acinetobacter* antigen.

2. A method according to claim 1, in which the *Acinetobacter* is one which presents to the mammal an antigen which exhibits molecular mimicry with the myelin of the mammal.

3. A method according to claim 1 or 2, in which the antibodies are indicative of prior infection by *Acinetobacter calcoaceticus*.

4. A method according to claim 1, 2, or 3, in which the antibodies tested for are antibodies which bind to an epitope present in or derived from the *Acinetobacter* species or to a prepared peptide sequence corresponding thereto.

5. A method according to any of claims 1 to 4, in which the disease tested for is bovine spongiform encephalopathy.

6. A method according to any of claims 1 to 4, in which the disease tested for is multiple sclerosis in humans.

7. A method according to any of claims 1 to 4, in which the disease tested for is Creutzfeldt-Jacob disease in humans.

8. A method according to any of the preceding claims in which antibodies are assayed and a positive result is indicated by levels of antibodies at least about two standard deviations above that of control samples.

9. A test kit for use with a method according to any of claims 1 to 8, in which the test antigen is the whole *Acinetobacter* organism or at least one prepared peptide sequence corresponding to an *Acinetobacter* epitope, said test kit including a secondary antibody against the human, bovine, or other mammalian IgA.

10. A method according to claim 1, 2, or 3, in which the antibodies tested for are antibodies which bind to a peptide sequence conformationally similar to an *Acinetobacter* epitope.

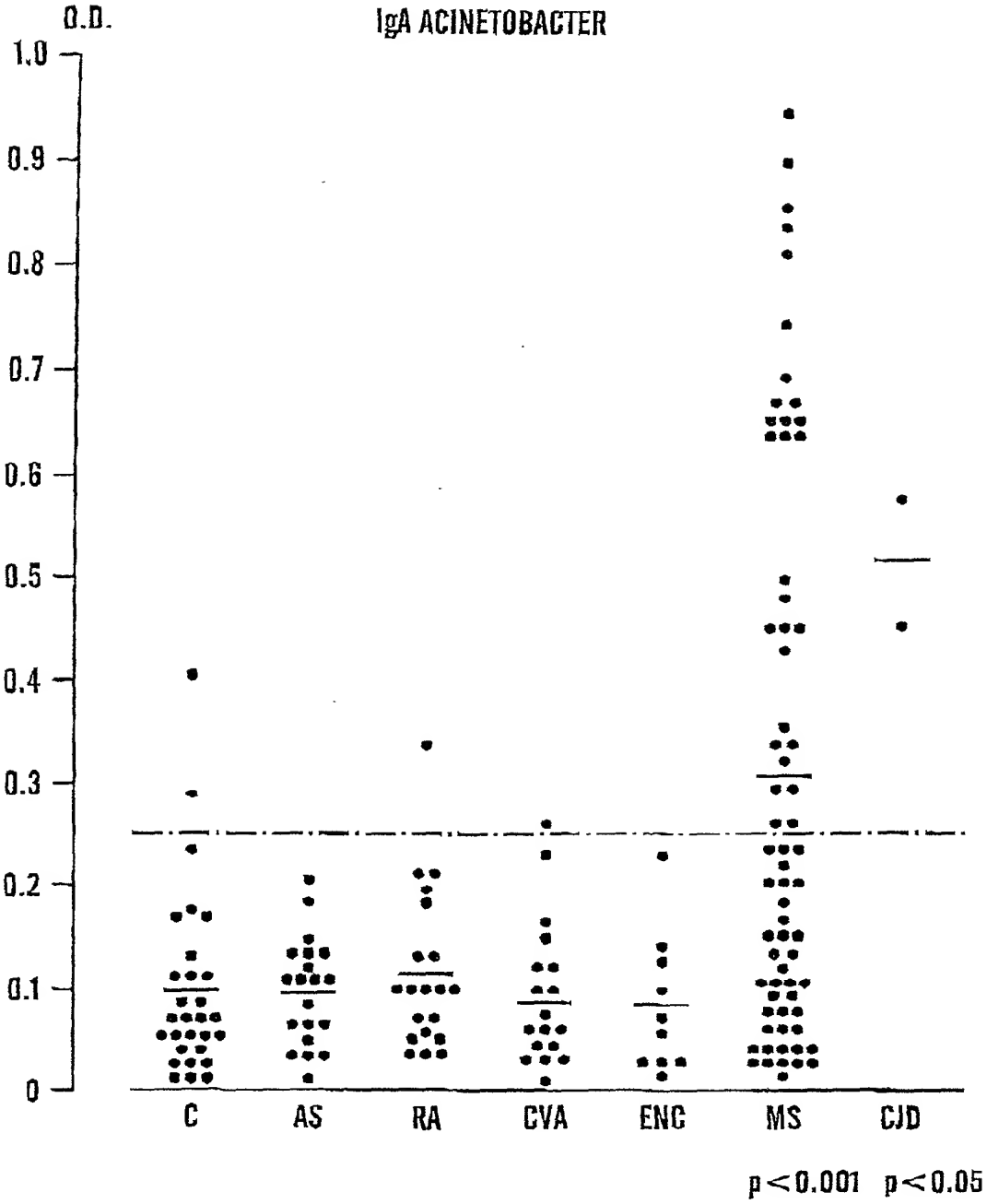
11. A method according to claim 10, in which the epitope is the peptide sequence ISRFAWGEV.

12. A method according to claim 10, in which the epitope contains the peptide sequence RFSAWGAE.

13. A test kit for use with a method according to claim 10, 11, or 12, in which the test antigen is a peptide sequence which is conformationally sufficiently similar to an *Acinetobacter* epitope to bind to the relevant antibodies, said test kit including a secondary antibody against the human, bovine, or other mammalian IgA.

14. A test kit according to claim 13, comprising a peptide having the sequence RFSAWGAE or ISRFAWGEV.

15. A test kit according to claim 9, or according to claim 13 or 14, in which the secondary antibody is a rabbit anti-human IgA or rabbit anti-bovine IgA.



LEGEND: IgA ANTIBODIES TO ACINETOBACTER BACTERIA, MEASURED BY ELISA IN HEALTHY CONTROLS (C) AND PATIENTS WITH ANKYLOSING SPONDYLITIS (AS), RHEUMATOID ARTHRITIS (RA), CEREBRO-VASCULAR ACCIDENTS (CVA), VIRAL ENCEPHALITIS (ENC), MULTIPLE SCLEROSIS (MS) AND CREUTZFELDT-JAKOB DISEASE (CJD). (p-VALUES INDICATE SIGNIFICANCE COMPARED TO CONTROLS)

Fig. 1

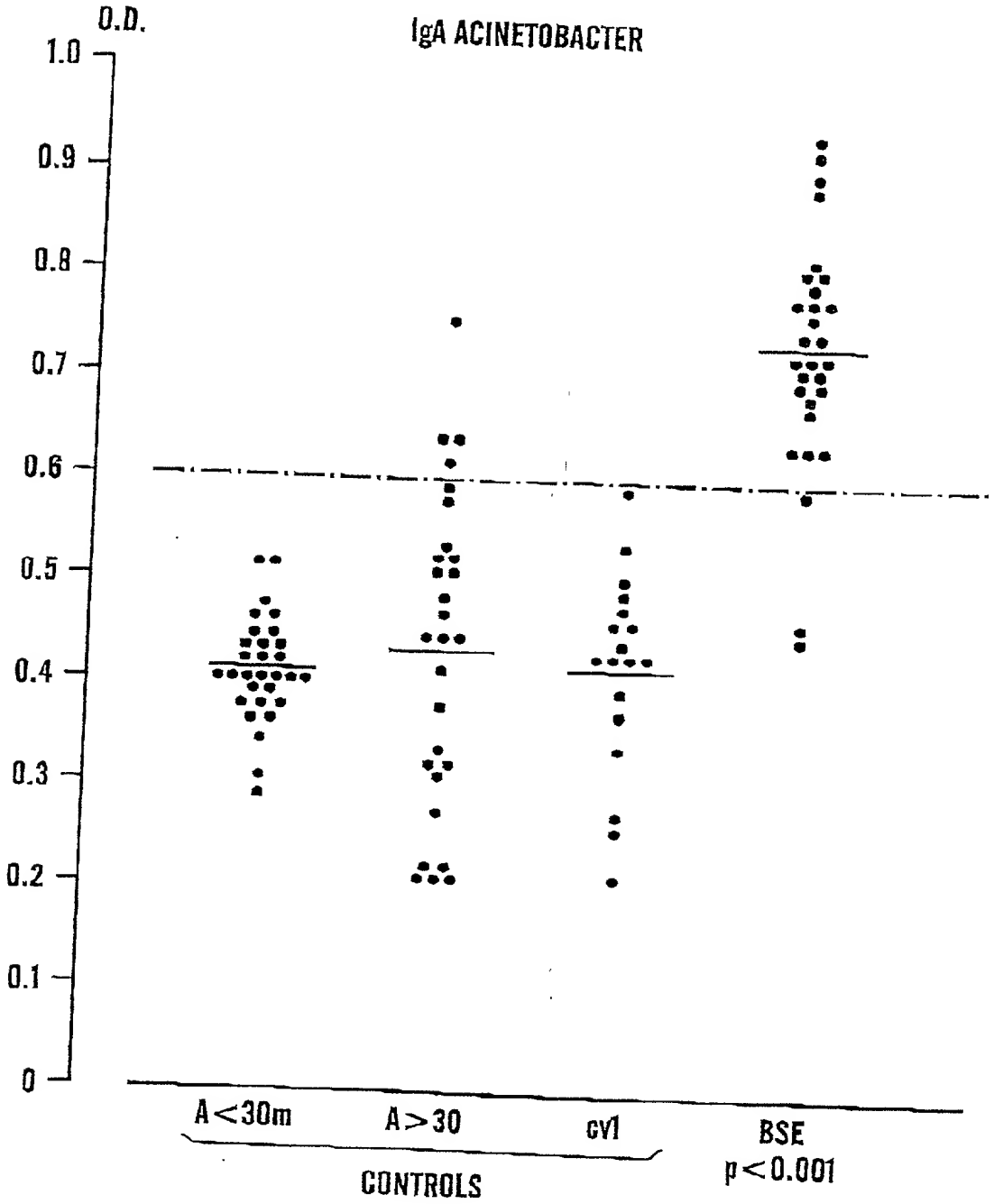

O.D.
IgA ACINETOBACTER
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
A<30m
A>30
cvl
BSE
p<0.001
CONTROLS

Fig.2

RULE 63 (37 C.F.R. 1.63)

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled – **DIAGNOSIS OF SPONGIFORM OR DE-MYELINATING DISEASE**. The specification was filed in the U.S. Patent Office **on September 18, 2000** under Serial No. **09/656,579** by way of entry into the national phase of Chapter II of International Application Number **PCT/GB99/00876** filed **March 19, 1999**, which in turn claims priority from British Patent Application Number **GB 9805913.2** filed **March 19, 1998.** This application is a continuation-in-part of U.S. patent application serial number **09/269,607** filed **July 26, 1999**. U.S. Patent Application Serial Number **09/269,607** is a national phase of Chapter II of International Patent Application Number **PCT/GB97/02267** filed **September 29, 1997**, which claims priority from British Patent Application Number **GB 9620195.9** filed **September 27, 1996**.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S):

Number	Country	Day/Month/Year Filed	Date First Laid Open or Published	Date Patented or Granted	Priority Claimed? Yes/No
PCT/GB99/00876	PCT	19 March 1999	23 September 1999		YES
GB 9805913.2	GB	19 March 1998			YES
PCT/GB97/02267	PCT	29 September 1997	02 April 1998		
GB 9620195.9	GB	27 September 1996			

I hereby claim domestic priority benefit under 35 U.S.C. 119/120/365 of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S)

Application No.	Day/Month/Year Filed	Status (Pending, Abandoned, Patented)	Priority Claimed? YES/NO
09/269,607	July 26, 1999	Pending	YES

RULE 63 (37 C.F.R. 1.63)

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled – DIAGNOSIS OF SPONGIFORM OR DE-MYELINATING DISEASE. The specification was filed in the U.S. Patent Office on September 18, 2000 under Serial No. 09/656,579 by way of entry into the national phase of Chapter II of International Application Number PCT/GB99/00876 filed March 19, 1999, which in turn claims priority from British Patent Application Number GB 9805913.2 filed March 19, 1998. This application is a continuation-in-part of U.S. patent application serial number 09/269,607 filed July 26, 1999. U.S. Patent Application Serial Number 09/269,607 is a national phase of Chapter II of International Patent Application Number PCT/GB97/02267 filed September 29, 1997, which claims priority from British Patent Application Number GB 9620195.9 filed September 27, 1996.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S):

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PCT/GB99/00876	PCT	19 March 1999	23 September 1999		YES
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PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S)

Application No.	Day/Month/Year Filed	Status (Pending, Abandoned, Patented)	Priority Claimed? YES/NO
09/269,607	July 26, 1999	Pending	YES

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint **Pillsbury Madison & Sutro LLP, 2550 Hanover Street, Palo Alto, California 94304-1115, telephone number (650) 233-4510** (to whom all communications are to be directed), and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete persons no longer with their firm and to act and rely on instructions from and communicate directly with the person/assignee who first sent this case to them and by whom I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or a below attorney in writing to the contrary.

Paul N. Kokulis	16773	Dale S. Lazar	28872	Timothy J. Klima	34852	W. Patrick Bengtsson	32456
Raymond F. Lippitt	17519	Glenn J. Perry	28458	Stephen C. Glazier	31361	Jack S. Barufka	37087
G. Lloyd Knight	17698	Kendrew H. Colton	30368	Paul F. McQuade	31542	Adam R. Hess	41835
Carl G. Love	18781	Paul E. White, Jr.	32011	Ruth N. Morduch	31044	William P. Atkins	38821
Kevin E. Joyce	20508	G. Paul Edgell	24238	Richard H. Zaitlen	27248	Paul L. Sharer	36004
George M. Sirilla	18221	Lynn E. Eccleston	35861	Roger R. Wise	31204	**David H. Jaffer**	**32243**
Donald J. Bird	25323	David A. Jakopin	32995	Jay M. Finkelstein	21082		
Peter W. Gowdey	25872	Mark G. Paulson	30793	Michael R. Dzwonczyk	36787		

1. INVENTOR'S SIGNATURE: (SEE ATTACHED) Date

Inventor's Name **Alan Ebringer** Country of Citizenship: United Kingdom

Address: **76 Gordon Road**

Ealing, London W5 2AR

hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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1. INVENTOR'S SIGNATURE: Alan Ehringer Date: 11 DEC 2000

Inventor's Name: Alan Ehringer

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